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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/427,873	10/27/99	BOYD	M 175912

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EXAMINER	
PARKIN, J	
ART UNIT	PAPER NUMBER
1648	8

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/427,873	Applicant(s) Boyd, M. R.
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *6 Aug 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Detailed Office Action

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the communication filed 06 August, 2001. Two declarations by Dr. Boyd also accompanied the communication. No amendments to the claims or new claims accompanied the submission. Claims 20-27 are currently under consideration.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20-27 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward therapeutic or prophylactic methods for inhibiting viral infection in a host through the administration of an antiviral peptide comprising at least nine contiguous amino acids of SEQ ID NO.: 2, which has been designated cyanovirin-N or CV-N. CV-N is a single 101 amino acid protein containing two intrachain disulphide bonds. The protein fails to display any significant sequence homology to other known proteins. It appears that CV-N binds directly to HIV-1 gp120. Other limitations specify that a viral envelope glycoprotein may also be administered with the antiviral peptide of interest. Applicant further indicates (see p. 4,

specification) that "yet another object of the present invention is to provide a method of treating an animal, in particular a human, infected by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-2 [sic-HIV-1] or HIV-2. A related object of the present invention is to provide a method of treating an animal, in particular a human, to prevent infection by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2."

As previously set forth, the disclosure failed to provide adequate guidance pertaining to a number of considerations. Those issues that are still of concern are listed as follows:

1) The disclosure clearly fails to provide sufficient guidance pertaining to the molecular determinants modulating the antiviral activity of SEQ ID NO.: 2. Applicant contends that only routine experimentation would be required to ascertain which peptides will work. The Examiner does not concur with this assessment. Clearly the applicant does not understand which regions of CV-N are required for the antiviral activity. Applicant is reminded that the claims encompass any contiguous nine amino acid stretch of CV-N. Thus, the skilled artisan would be required to synthesize and screen an inordinate number of peptides. The disclosure fails to point the skilled artisan toward any particular direction. For instance, is the amino terminus critical for activity? What about amino acids 30-39? What about the carboxyl terminus. This is nothing but an invitation to further undue experimentation.

2) The disclosure clearly fails to teach which polypeptide fragments of "at least nine contiguous amino acids" contain the requisite determinants that are required for antiviral activity. Applicant contends once again that only routine experimentation would be required to ascertain which nine contiguous amino acids will work. The Examiner does not concur with this assessment. Clearly the applicant does not understand which regions of CV-N are required for the antiviral activity. Applicant is reminded that

the claims encompass any contiguous nine amino acid stretch of CV-N. Thus, the skilled artisan would be required to synthesize and screen an inordinate number of peptides. The disclosure fails to point the skilled artisan toward any particular direction. For instance, should the amino terminal 10 amino acids be utilized? What about the amino terminal 20, 30, or 40 amino acids? Should the carboxy terminal 10, 20, 30, or 40 amino acids be employed? Which peptide fragments can reasonably be expected to contain the determinants modulating the antiviral activity of the protein? The disclosure fails to provide appropriate guidance pertaining to this matter. Absent further guidance on the subject, the skilled artisan cannot make a reasonable determination as to which consecutive amino acids should be included in any given polypeptide.

3) It was previously argued that the disclosure fails to provide any guidance pertaining to the binding specificity of CV-N, or polypeptide fragments thereof. Applicant provided declaratory data illustrating that CV-N is also capable of binding to HSV-gC, both HIV-1 gp120 and gp41, and to a lesser extent, Ebola virus surface glycoprotein. However, the declaration fails to provide any guidance pertaining to the binding specificity of CV-N. It appears that CV-N binds to oligosaccharides but no direction is provided pertaining to the specificity of the binding interaction. It is well-known in the art that viral envelope protein glycosylation patterns are quite variable. Thus, it is not readily manifest that all viruses will display the same affinity for CV-N. While it appears that CV-N binds to gp1-Z, gp120, and gp41 rather strongly, and sgpZ only moderately, it is not clear that this binding interaction can be extended to all other viruses. Moreover, the disclosure and declaration are both silent pertaining to those nine contiguous amino acids that modulate this binding interaction.

4) The prior art teaches that the development of HIV-1 antivirals has been a largely unsuccessful endeavor (Saunders, 1992; Wilting

and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran *et al.*, 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997) due to a number of factors such as the lack of suitable animal models and the quasispecies nature of HIV. Applicant argues that the specification fully enables the claimed invention. It was argued that the *in vitro* assay relied upon is widely accepted as being predictive of *in vivo* and clinical results. Contrary to applicant's assertion, the *in vitro* assay relied upon is clearly not a reliable predictor of clinical efficacy. It has been well-documented that simple *in vitro* screening assays are not predictive of clinical efficacy (Saunders, 1992; Wiltink and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran *et al.*, 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997). As Whittle and Blundell (1994) note, the rational design of antivirals is a difficult process. Random *in vitro* drug screening assays are only a rudimentary first step in the identification of efficacious antiviral agents. As the authors conclude, "while it [structure-based drug design] can be of great use in the initial process of identifying ligands with improved affinity and selectivity *in vitro*, it can usually say very little about other essential aspects of the drug discovery process, e.g., the need to achieve an adequate pharmacokinetic profile and low toxicity *in vivo*." Accordingly, the results obtained from this assay do not constitute an appropriate working embodiment. Thus, the *in vitro* tissue culture model relied upon is hardly predictive of clinical efficacy.

5) Applicant is reminded that the claims are also of excessive breadth. The claims broadly encompass methods of treating any viral infection and could include DNA viruses, RNA viruses, or retroviruses of vastly different genotypic compositions and phenotypic activities. Moreover, the claims broadly encompass methods that may employ various CV-N polypeptide fragments.

However, as noted *supra*, the disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the antiviral and binding activities of the cyanovirin. Absent such guidance, the skilled artisan has only been extended an undue invitation to further experimentation.

6) It was previously argued that the disclosure failed to provide a sufficient number of working embodiments that would enable the full breadth of the claimed invention. Applicant contends that the specification is fully enabling and notes that data was obtained from a macaque model. Applicant provided an earlier Declaration under 37 C.F.R. § 1.132 involving data obtained from an SIV model. A gel comprising CV-N was applied intrarectally or intravaginally and an inoculant comprising the virus SHIV89.6P administered. As previously set forth, appropriately drafted claim language directed toward this embodiment would be acceptable. However, the SIV/SHIV model is not an accurate predictor of clinical efficacy (Rice and Bader, 1995). As Rice and Bader (1995) conclude, "the final test of a drug's efficacy comes in the clinical experience."

There were a number of other concerns pertaining to the declaratory data earlier provided. The declaration failed to address a number of important issues. For instance, the declaration was silent pertaining to challenge studies involving different HIV-1 and -2 isolates, as well as, other viral isolates (i.e., FIV, BIV, EIAV, CAEV, HSV, CMV, HTLV, etc.). Insufficient guidance was provided concerning the ability of CV-N to inactivate physiologically relevant concentrations of HIV-1, HIV-2, or other viruses. The declaration was also silent pertaining to the pharmacological and therapeutic profile of CV-N. The experimental model employed failed to measure reductions in viral load. It has been well-documented that HIV-1-infected patients produce upwards of 1×10^{10} virions per day. It seems unlikely that adequate concentrations of the CV-N protein can be maintained over sufficient periods of time to provide any meaningful effect. The

experimental model employed did not provide any guidance pertaining to the pharmacological properties of the peptide. Many compounds fail to display clinical efficacy because of pharmacological concerns (i.e., binding and inactivation by serum proteins, rapid clearance rate, poor circulating half-life, inability to target the tissue of interest [i.e., the lymphatic compartment]). However, none of these properties were addressed in the declaration. Thus, the skilled artisan cannot make an meaningful deductions pertaining to the therapeutic properties of the antiviral composition. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Obviousness-Type Double Patenting

4. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

5. A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee

must fully comply with 37 C.F.R. § 3.73(b).

6. Claims 20 and 21 stand **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-24 of copending Application Serial No. 09/428,275. Applicants have indicated that this rejection will be addressed when allowable subject matter has been agreed upon.

7. Claims 20 and 21 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876. Applicants contend that the claims of the '876 patent do not suggest administering an antiviral agent to a host for therapeutic or prophylactic purposes. This argument is not deemed to be persuasive. The claims of the '876 patent involve a contact step between the virus and antiviral agent. The claims do not specify in what context this contact step occurs. Thus, the claims could reasonably encompass *in vitro*, *in vivo*, and clinical applications and the claims of the instant application fall within the scope of the '876 patent. Accordingly, the claims are not patentably distinct from each other.

Finality of Office Action

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R.**

§ 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Correspondence

9. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

10. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

31 October, 2001

LAURIE SCHEINER
PRIMARY EXAMINER

Non-nucleoside inhibitors of HIV reverse transcriptase: screening successes--clinical failures. Saunders J. (Department of Medicinal Chemistry II, Glaxo Group Research, Greenford, Middlesex, UK.) DRUG DESIGN AND DISCOVERY, (1992 Jul) 8 (4) 255-63. Ref:19. Journal code:A5B; 9200627. ISSN: 1055-9612. Pub. country: Switzerland. Language: English.

AB A little less than two years ago, the first report describing non-nucleoside inhibitors of HIV reverse transcriptase (RT) led to the high anticipation that a range of new drugs could soon be available for the treatment of AIDS. The intervening period has given rise to several such agents but recent clinical trial data has indicated this optimism to be premature. This short review seeks to trace the brief history of the drug discovery process and to assess whether there are lessons to be learnt from the episode.